PATENT SPECIFICATION (11) 1351569

1351569

(21) Application No. 22618/72 (22) Filed 15 May 1972

(44) Complete Specification published 1 May 1974

(51) International Classification C07D 99/02//A61K 27/00

(52) Index at acceptance

C2C 1562 1590 215 246 247 250 252 255 25Y 28X 305 30Y 313 31Y 337 351 352 364 36Y 386 388 43X 500 50Y 624 625 672 761 765 790 79Y TN

(72) Inventors ISAO SATODA, MASAHIRO TAKAYA TORIZO TAKAHASHI and YOSHIFUMI MAKI

(19)

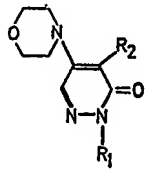
(54) 2-ALKYL-4-ALKOXY-5-MORPHOLINO-3(2H)-PYRIDAZINONES AND THEIR METHOD OF PREPARATION

(71) We, MORISHITA PHARMACEUTICAL CO., LTD., a Japanese body corporate, No. 29, 4-chome, Dosho-machi, Higashi-ku, Osaka-shi, Japan, do hereby

declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel 2-alkyl - 4 - alkoxy - 5 - morpholino - 3(2H) - pyridazinones, their method of preparation and their pharmaceutical application.

According to the present invention there is provided a 2-alkyl-4-alkoxy-5-morpholino-3(2H)-pyridazinone of the general formula:



(I)

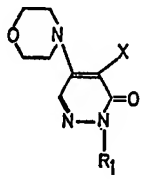
wherein R_1 is an alkyl group, and R_2 is an alkoxy group.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl and amyl, and preferred alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and pentoxy.

The compounds of the present invention are particularly suitable in the treatment of catarrh, since they have a high anodyne power and a very low toxic effect. More particularly, 2 - methyl - 4 - ethoxy - 5 - morpholino - 3(2H)-pyridazinone has very low toxic property (an L D_{50} of higher than 1000 mg/kg when applied to the abdominal cavity of mouse), and a high anodyne power (three times as much as that of the Aminopyrine when measured by the improved Haffner method).

Also according to the invention, there is provided a pharmaceutical composition comprising a compound of the general formula (I) together with a pharmaceutically-acceptable carrier.

The compounds of the present invention may be prepared in a high yield by reacting a 2 - alkyl - 4 - halogeno - 5 - morpholino - 3(2H)-pyridazinone of the general formula:

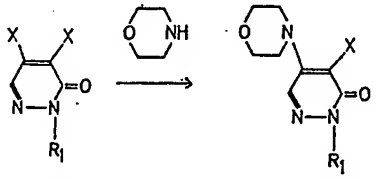


(II)

wherein R_1 is an alkyl group and X is a halogen atom, with an alkali metal alcoholate, which alcoholate contains an alkoxy group corresponding to R_2 in formula (I), with heating, preferably at about the reflux temperature of an alkyl alcohol for 2—8 hours.

The 2 - alkyl - 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinones of the general formula (II), may be prepared by either of the two following processes:

(1) According to the reaction:



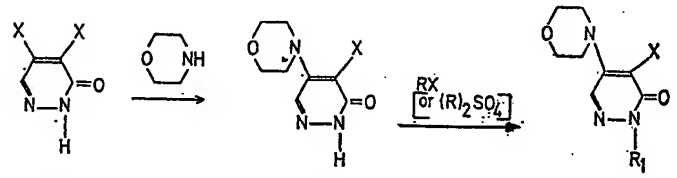
(III) (II)

wherein, R_1 is an alkyl group and X is a halogen atom.

The 2 - alkyl - 4,5 - dihalogeno - 3(2H) - pyridazinone of the general formula (III) is reacted with morpholine with heating and with

or without solvent for one to ten hours, to produce the 2 - alkyl - 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (II). As solvent in the above process may be utilised, for example, water, methanol, ethanol, propanol, methyl cellosolve, ethyl cellosolve or propylene-glycol. (Cellosolve is a Registered Trade Mark). The duration and conditions for the reaction depend upon selection of the solvent and the boiling point thereof. The reaction is preferably carried out at the reflux temperature of the solvent utilised. If ethanol is used as solvent, the desired product, in substantially quantitative yield, is obtained by carrying out the reaction for five hours at 90°C. In the absence of a solvent, the desired product is obtained by carrying out the reaction for one to three hours at about 140°C.

(2) According to the reaction:



(IV) (V) (II)

As starting material for this process there is utilised a 4,5 - dihalogeno - 3(2H) - pyridazinone of the general formula (IV), which may be prepared by reacting hydrazine hydrate with a mucohalogen acid under heating, which basic materials are obtained at low cost. In contrast thereto the 2-alkyl-4,5-dihalogeno - 3(2H) - pyridazinone of the general formula (III) utilised in process (I) above, is prepared by reacting a mucohalogen acid with an alkylhydrazine under heating. The alkyl hydrazine is difficult to synthesise even in low yield.

The compound of general formula (IV) is reacted with morpholine to quantitatively yield a 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (V). Then the compound (V) is reacted under heating with an alkyl halide in the presence of an alkali metal methylate, or is reacted under heating with a dialkylsulphate in the presence of an aqueous alkali to obtain a 2-alkyl-4-halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (II) in high yield and at low cost.

More specifically a 4,5-dihalogeno-3(2H)-pyridazinone of the general formula (IV) is first quantitatively produced by reacting mucohalogen acid with hydrazine hydrate in aqueous alcohol or an aqueous mineral acid under heating at 90°C to 140°C for 2 to 3 hours. Then the compound of general formula (IV) is reacted with morpholine with or without the presence of an alcohol or water as solvent under heating at 90°C to 180°C for 6 to 15 hours to quantitatively synthesize a 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (V).

The compound of the general formula (V) is then reacted with an alkyl halide, which corresponds to an alkyl group of the 2-alkyl-4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (II), in the presence of an alkali metal methylate, under heating at 80°C to 100°C for 3 to 8 hours, whereby there is obtained a 2-alkyl-4-halogeno-5 - morpholino - 3(2H) - pyridazinone of the general formula (II) in a yield of 70 to 90%.

As the alkyl halide utilisable in the above process, there may be exemplified methyl iodide, methyl bromide, methyl chloride, ethyl iodide, ethyl bromide, normal propyl bromide, isopropyl chloride, normal butyl bromide, isobutyl bromide, isobutyl chloride, secondary butyl chloride, normal amyl bromide and isoamyl bromide.

The 2 - alkyl - 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula (II) may also be prepared by adding one mole of a 4-halogeno-5-morpholino-3(2H)-pyridazinone of the general formula (V) to an aqueous alkali consisting of 10 moles of water and 1.5 to 3 moles of alkali, the resultant solution being heated at 130°C to 150°C with agitation, and into which is dropped 1.5 to 3 moles of dialkylsulphate. The above reaction is continued for 3 to 7 hours at the above temperature, and once the reaction has finished, the product may be extracted by means of chloroform to produce the 2-alkyl-4-halogeno-5 - morpholino - 3(2H) - pyridazinone of the general formula (II) in a yield of 60 to 85%.

As the alkali utilisable in the above process, there may be exemplified sodium hydroxide and potassium hydroxide, and as the dialkyl sulphate there may be exemplified dimethyl sulphate and diethyl sulphate.

Figs. 1 and 2 show the infrared absorption spectra of 2 - methyl - 4 - ethoxy - 5 - morpholino - 3(2H) - pyridazinone, and 2-ethyl-4-ethoxy - 5 - morpholino - 3(2H) - pyridazinone, respectively which compounds have been prepared by a process described above.

The invention will be further illustrated with reference to the following Examples.

Example 1

6 g of 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 60 ml of ethanol containing 901 mg of metallic sodium, and the resultant mixture is heated under reflux within a water bath for three hours. Upon completion of the reaction, the solvent is distilled off to leave a residue, which is dissolved in water, and the product is extracted therefrom by means of chloroform. The chloroform layer is washed with water and dried, and the chloroform is then distilled off. The residue obtained is recrystallized from isopropyl ether, to yield 5.0 g of 2-methyl-4-ethoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of colourless scale like crystals having a melting point of 90°C to 91°C.

Halogen detection in this compound according to Beilstein's test has proved negative.

Empirical formula = $C_{11}H_{17}O_3N_3$

Elementary analysis:

	C	H	N
Calculated %	55.21	7.16	17.57
Found %	55.05	7.22	17.53

and the infrared absorption spectrum shows 1625 cm^{-1} (C=O group) (Fig. 1).

The 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, used as starting material may be prepared by the following process:

10 g of 2 - methyl - 4,5 - dichloro - 3(2H) - pyridazinone is added to 100 ml of ethanol containing 15 g of morpholine, and the resultant mixture in water heated under reflux in a water bath for 5 hours. Once the reaction is completed the solvent is distilled off to leave a residue, which is dissolved in water and extracted therefrom by means of chloroform. The chloroform layer is washed with water and dried, and the chloroform is distilled off. The residue obtained is recrystallized from a mixture of ethanol and isopropyl ether to yield 10 g of 2-methyl-4-chloro-5-morpholino-3(2H)-pyridazinone in the form of colourless needle crystals having a melting point of 134°C to 135°C.

Halogen detection in this compound according to Beilstein's test has proved positive.

Empirical formula = $C_9H_{12}N_3O_2Cl$,

Elementary analysis:

	C	H	N
Calculated %	47.06	5.27	18.30
Found %	46.85	5.27	18.24

and in the infrared absorption spectrum shows 1648 cm^{-1}, 1632 cm^{-1} (C=O group).

Example 2

1 g of 2 - ethyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 12 ml of sodium methylate containing 123 mg of metallic sodium, and the resultant mixture is heated under reflux in a water bath for three hours. Once the reaction is completed, the solvent is distilled off to leave a residue which is dissolved in water, and the product is extracted therefrom by means of chloroform. The chloroform layer is then washed with water and dried, and the chloroform is then distilled off. The oily residue obtained is distilled off at 143°C to 145°C under 0.04 mm Hg pressure to yield 0.7 g of 2-ethyl-4-methoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of a light yellow oil.

The Beilstein's test of this compound has proved negative, and the ferric chloride reaction has also proved negative.

Empirical formula = $C_{11}H_{17}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated %	55.21	7.16	17.56
Found %	54.95	7.28	17.44

and the infrared absorption spectrum shows 1616 cm^{-1} (C=O group) (Fig. 2).

The starting material, 2-ethyl-4-chloro-5-morpholino - 3(2H) - pyridazinone may be prepared by the following process:

10 g of 2-ethyl-4,5-dichloro-3(2H)-pyridazinone is added to 50 ml of morpholine, and the resultant mixture is heated under reflux in a water bath at 145°C for one hour. Once the reaction is completed, any excess morpholine is distilled off under a reduced pressure. Water is added to the residue which is extracted by means of chloroform. The residue is subsequently washed with water and dried and the solvent is distilled off. The residue is recrystallized from isopropyl ether to yield 8.0 g of 2 - ethyl - 4 - chloro - 5 - morpholino - 3(2H)-pyridazinone in the form of colourless scale-like crystals having a melting point of 79°C to 81°C.

The Beilstein's test on this compound has proved positive, and the ferric chloride reaction proved negative.

Empirical formula = $C_{10}H_{14}O_2N_3Cl$,

Elementary analysis:

	C	H	N
Calculated %	49.29	5.79	17.24
Found %	48.96	5.48	17.17

and the infrared absorption spectrum shows 1637 cm^{-1} (C=O group).

Example 3

1.5 g of 2-normal propyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 18 ml of ethyl alcohol containing 200 mg of metallic sodium, and the resultant mixture is heated under reflux in a water bath for 12 hours. Once the reaction is completed, the solvent is distilled off under a reduced pressure to leave a residue, which is dissolved in about

15 ml of water and extracted by means of chloroform. The chloroform layer is washed with water, dried and distilled to remove the chloroform, and the oily residue is then distilled under reduced pressure to yield 1.0 g of 2-normal propyl - 4 - ethoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of a colourless transparent oil having a boiling point of 157°C to 160°C (0.46 mm Hg).

Halogen detection in this compound by the Beilsteins's test has proved negative.

Empirical formula=$C_{13}H_{21}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated:	58.41	7.92	15.72
Found %	58.28	8.22	15.82

and the infrared absorption spectrum shows 1630 cm^{-1} (C=O group).

The 2-normal propyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, utilisable as starting material for the above process may be prepared in the following manner:

10 g of 2-normal propyl - 4,5 - dichloro - 3(2H) - pyridazinone is added to 100 ml of ethanol containing 15 g of morpholine, and the resultant mixture is heated under reflux for six hours at about 95°C. Once the reaction is completed, the solvent is distilled off under reduced pressure, and the residue obtained is dissolved in water and is then extracted by means of chloroform. The chloroform layer is washed with water, dried and distilled off under reduced pressure, and the residue is recrystallized from isopropyl ether to yield 9.5 g of 2-normal propyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, in the form of colourless scale-like crystals having a melting point of 84°C to 85°C.

Halogen detection in this compound by Beilstein's test has proved positive.

Empirical formula=$C_{11}H_{16}O_2N_3Cl$

Elementary analysis:

	C	H	N
Calculated %	51.26	6.21	16.31
Found %	51.11	6.15	16.61

and the infrared absorption spectrum shows 1642 cm^{-1} (C=O group).

Example 4

1.2 g of 2 - isopropyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 12 ml of ethyl alcohol containing 161 mg of metallic sodium, and the resultant mixture is heated under reflux at 95°C to 100°C for 12 hours. Once the reaction is completed the solvent is distilled off and the residue is similarly processed as in Example 3, to yield 1.0 g of 2 - isopropyl - 4 - ethoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of a colourless transparent oil having a boiling point of 147°C to 149°C (0.08 mm Hg).

Empirical formula=$C_{13}H_{21}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated %	58.41	7.92	15.72
Found %	57.92	8.04	15.80

and the infrared absortion spectrum shows 1630 cm^{-1} (C=O group).

The 2 - isopropyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, which is utilised as starting material for the above process, may be prepared by reacting 2-isopropyl-4,5-dichloro - 3(2H) - pyridazinone with morpholine in alcohol under conditions similar to those of Example 3, to yield 2-isopropyl-4-chloro-5-morpholino - 3(2H) - pyridazinone in the form of a colourless transparent oil having a boiling point of 169°C to 171°C (0.3 mm Hg) in a yield of 80%.

Empirical formula=$C_{11}H_{16}O_2N_3Cl$,

Elementary analysis:

	C	H	N
Calculated %	51.26	6.21	16.31
Found %	51.01	6.45	16.27

and the infrared absorption spectrum shows 1660 cm^{-1} (C=O group).

Example 5

2 g of 2-normal butyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 20 ml of ethanol containing 245 mg of metallic sodium and the resultant mixture is heated under reflux in a water bath for 12 hours. Once the reaction is completed, the solvent is distilled off and the residue thereof is processed in a similar manner as in Example 3, to yield 1.62 g of 2-normal butyl-4-ethoxy-5 - morpholino - 3(2H) - pyridazinone in the form of a colourless transparent oil having a boiling point of 164°C to 165°C.

Empirical formula =$C_{14}H_{23}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated %	59.70	8.24	14.94
Found %	59.60	8.25	14.71

and the infrared absorption spectrum shows 1640 cm^{-1} (C=O group).

The 2-normal butyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone which is used as starting material for the above process, may be prepared in the following manner:

10 g of 2-normal butyl - 4,5 - dichloro - 3(2H) - pyridazinone is added to 50 ml of morpholine, and the resultant mixture is heated under reflux at 145°C for 1 hour. Once the reaction is completed, any excess morpholine is distilled off under reduced pressure, and the residue is dissolved in 50 ml of water, and

the resultant solution is extract by means of chlorofom. The chloroform layer is washed with water, and dried. The residue is distilled off under reduced pressure to yield 8.5 g of 2-normal butyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone in the form of a colourless transparent oil having a boiling point of 188°C to 190°C (0.18 mm Hg).

Empirical formula=$C_{12}H_{18}O_2N_3Cl$

Elementary analysis:

	C	H	N
Calculated %	53.03	6.67	15.46
Found %	52.81	6.85	15.73

and the infrared absorption spectrum shows 1660 cm^{-1} and 1640 cm^{-1} (C=O group).

Example 6

1.2 g of 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 15 ml of methanolic sodium methylate containing 156 mg of metallic sodium, and the resultant mixture is heated under reflux in a water bath for three hours. Once the reaction is completed, the solvent is distilled off, and the residue is dissolved in water, and is extracted by means of chloroform. The chloroform layer is then washed with water and dried. The residue is recrystallized from isopropyl ether to yield 1.0 g of 2-methyl-4-methoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of colourless needle crystals having a melting point of 70°C to 72°C.

The Beilstein test on this compound has proved negative, and the ferric chloride test have proved negative.

Empirical formula=$C_{10}H_{15}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated %	53.32	6.71	18.66
Found %	53.07	6.64	18.52

and the infrared absorption spectrum shows 1650 cm^{-1} (C=O group).

The compound 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone which has been employed as starting material for the above process may be prepared in the following manner:

3 g of 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 25 ml of methyl alcohol containing 384 mg of metallic sodium. 3 g of methyl iodide is added to the resultant solution and the mixture is then heated under reflux in a water bath for three hours. Once the reaction is completed the solvent is distilled off, and after having been cooled, 30 ml of water is added to the residue, which is then extracted by means of chloroform. The chloroform layer is washed with water and dried over sodium sulphate and evaporated to dryness to yield 2.2 g of 2-methyl-4-chloro-5-morpholino - 3(2H) - pyridazinone in the form of coarse crystals having a melting point of 127°C to 132°C. The compound may be recrystallized from a mixture of ethyl alcohol and isopropyl ether to yield colourless needle crystals having a melting point of 134°C to 135°C.

Empirical formula=$C_9H_{12}O_2N_3Cl$

Elementary analysis:

	C	H	N
Calculated %	47.06	5.27	18.30
Found %	46.85	5.27	18.23

and the infrared absorption spectrum shows 1630 cm^{-1} (C=O group).

Further, the 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, which is the starting material for preparing the 2-methyl-4-chloro-5 - morpholino - 3(2H) - pyridazinone may be produced in the following manner:

24 g of mucochloric acid is added to 80 ml of ethyl alcohol and 8.9 g of an 80% aqueous solution of hydrazine hydrate is added thereto, to which is further added 10 ml of an aqueous solution of 10% of hydrochloric acid, and the resultant solution is heated under reflux in a water bath at 95°C for three hours. Once the reaction is completed the product may be cooled to yield 22 g of 4,5-dichloro-3(2H)-pyridazinone in the form of colourless crystals having a melting point of 204°C to 205°C.

Then 6 g of the 4,5-dichloro-3(2H)-pyridazinone and 11 g of morpholine are added to 60 ml of ethyl alcohol, and the resultant mixture is heated under reflux in a water bath for 7 hours. After cooling, crystals form from the above solution, and are recovered by filtering. The crystals are washed with a small volume of water, to yield 8.2 g of 4-chloro-5-morpholino - 3(2H) - pyridazinone in the form of colourless crystals having a melting point of 231°C to 232°C.

Empirical formula=$C_8H_{10}O_2N_3Cl$

Elementary analysis:

	C	H	N
Calculated %	44.54	4.64	19.48
Found %	44.29	4.73	19.31

and the infrared absorption spectrum shows 1650 cm^{-1} (C=O group).

Example 7

1 g of 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone, which has been prepared by a process similar to that described in Example 6, is added to 15 ml of normal propyl alcohol containing 130 mg of metallic sodium and the resultant solution is heated in a water bath at 120°C, for 5 hours. After the reaction is completed, the solvent is distilled off. The residue thus produced is dissolved in water, and then extracted by means of chloro-

form. The chloroform layer is then washed with water and dried, whereby an oily residue is produced. Such oily residue is distilled under reduced pressure to yield 0.85 g of 2 - methyl - 4 - normal propoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of a light yellow oil having a boiling point of 183°C (3.0 mm Hg).

The Beilstein test of the compound proved negative and the ferric chloride test also proved negative.

Empirical formula=$C_{12}H_{19}O_3N_2$

Elementary analysis:

	C	H	N
Calculated %	56.9	7.56	16.59
Found %	56.68	7.48	16.37

and the infrared absorption spectrum shows 1645 cm^{-1} and 1630 cm^{-1} (C=O group).

Example 8

1 g of 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone is added to 15 ml of methanolic sodium normal butylate containing 160 mg of metallic sodium and the resultant solution is heated under reflux at 145°C to 150°C for 4 hours. Once the reaction is completed, the solvent is distilled off. Water is added to the residue and the residue is extracted by means of chloroform. The chloroform layer is then washed with water, and the residue is dried and distilled off at 189°C to 190°C under reduced pressure, 3.2 mm Hg, to yield 0.9 g of 2-methyl-4-normal butoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of a light yellow oil.

The Beilstein test on this compound has proved negative.

Empirical formula=$C_{13}H_{21}O_3N_3$,

Elementary analysis:

	C	H	N
Calculated %	58.41	7.92	15.72
Found %	57.91	8.29	15.46

and the infrared absorption spectrum shows 1643 cm^{-1} (C=O group).

The 2 - methyl - 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone utilised as starting material in the above process may be prepared in the following manner:

21 g of 4 - chloro - 5 - morpholino - 3(2H) - pyridazinone prepared in a manner similar to that of Example 6, is added to an aqueous alkaline solution consisting of 10 g of sodium hydroxide dissolved in 180 ml of water, and the resultant mixture is heated under reflux at 140°C and 31 g of dimethyl sulphate is then added thereto dropwise over a period of about 30 minutes whilst agitating the solution. Once the addition of dimethyl sulphate is completed, the solution is heated at the same temperature for 6 hours whilst continuing the agitation. After cooling the solution is extracted by means of chloroform, is dried over sodium sulphate, then distilled off to dryness, and the residue is recrystallized from a mixture of ethyl alcohol and isopropyl ether to yield 14.5 g of 2-methyl-4-chloro-5-morpholino - 3(2H) - pyridazinone in the form of colourless needle crystals having a melting point of 134°C to 135°C.

Empirical formula=$C_9H_{12}O_2N_3Cl$

Elementary analysis:

	C	H	N
Calculated %	47.06	5.27	18.30
Found %	46.81	5.43	18.27

and the infrared absorption spectrum shows 1630 cm^{-1} (C=O goup).

Example 9

1.8 g of 2 - ethyl - 4 - chloro - 3 - morpholino - 3(2)H) - pyridazinone prepared by the process described in Example 8 is added to 20 ml of ethanol containing 221 mg of metallic sodium and the resultant mixture is heated under reflux in a water bath for three hours. Once the reaction is completed, the solvent is distilled off. The residue is dissolved in water and is extracted by means of chloroform. The chloroform layer is washed with water and dried. The residue is recrystallized from isopropyl ether to yield 1.35 g of 2-ethyl-4 - ethoxy - 5 - morpholino - 3(2H) - pyridazinone in the form of colourless needle crystals having a melting point of 61°C to 64°C.

The Beilstein test on this compound has proved negative.

Empirical formula=$C_{12}H_{19}O_3N_3$,

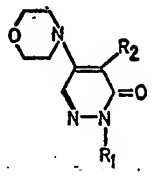
Elementary analysis:

	C	H	N
Calculated %	56.90	7.56	16.59
Found %	56.71	7.42	16.49

and the infrared absorption spectrum shows 1640 cm^{-1} (C=O group (Fig. 2).

WHAT WE CLAIM IS:—

1. A 2 - alkyl - 4 - alkoxy - 5 - morpholino - 3(2H) - pyridazinone of the general formula:



(I)

wherein R_1 is an alkyl group and R_2 is an alkoxy group.

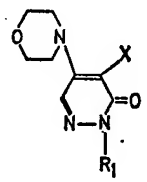
2. A compound as claimed in claim 1, in which R_1 is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl or amyl group.

3. A compound as claimed in claim 1 or 2, in which R_2 is a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy or pentoxy group.

4. A compound as claimed in claim 1, substantially as hereinbefore described and exemplified.

5. A pharmaceutical composition comprising a compound as claimed in any preceding claim together with a pharmaceutically-acceptable carrier.

6. A process for the preparation of a compound as claimed in claim 1, comprising reacting a 2 - alkyl - 4 - halogeno - 5 - morpholino - 3(2H) - pyridazinone of the general formula,



wherein R_1 is an alkyl group and X is a halogen atom, with an appropriate alkali metal alcoholate with heating.

7. A process as claimed in claim 6, in which the reaction is carried out at about the reflux temperature of an alkyl alcohol for 2—8 hours.

8. A process as claimed in claim 6, substantially as hereinbefore described and exemplified.

9. A 2 - alkyl - 4 - alkoxy - 5 - morpholino - 3(2H) - pyridazinone whenever prepared by a process as claimed in any one of claims 6 to 8.

POTTS, KERR & CO.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

1351569 COMPLETE SPECIFICATION
2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*
Sheet 1

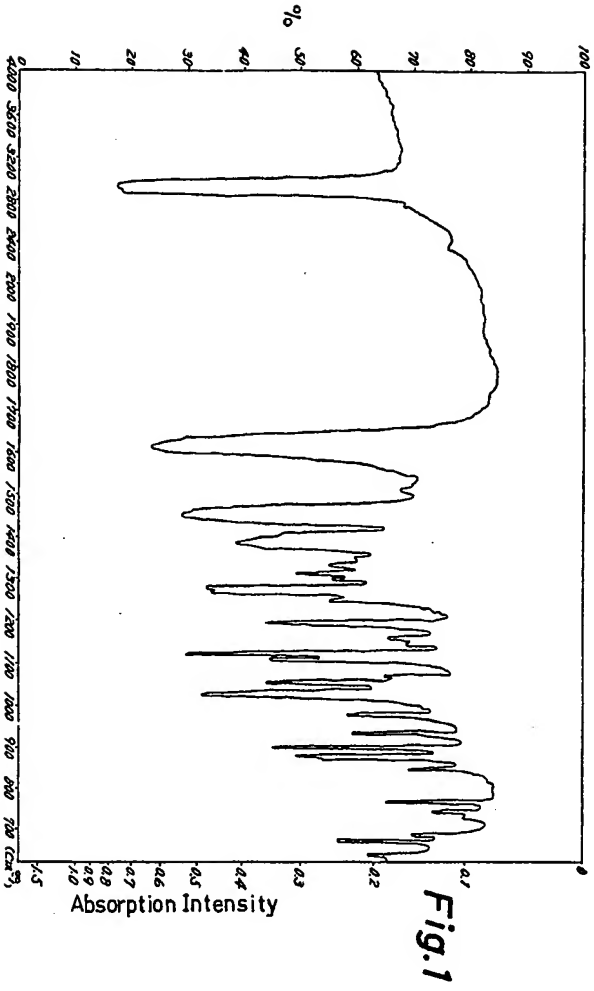


Fig. 1

1351569 COMPLETE SPECIFICATION

2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 2

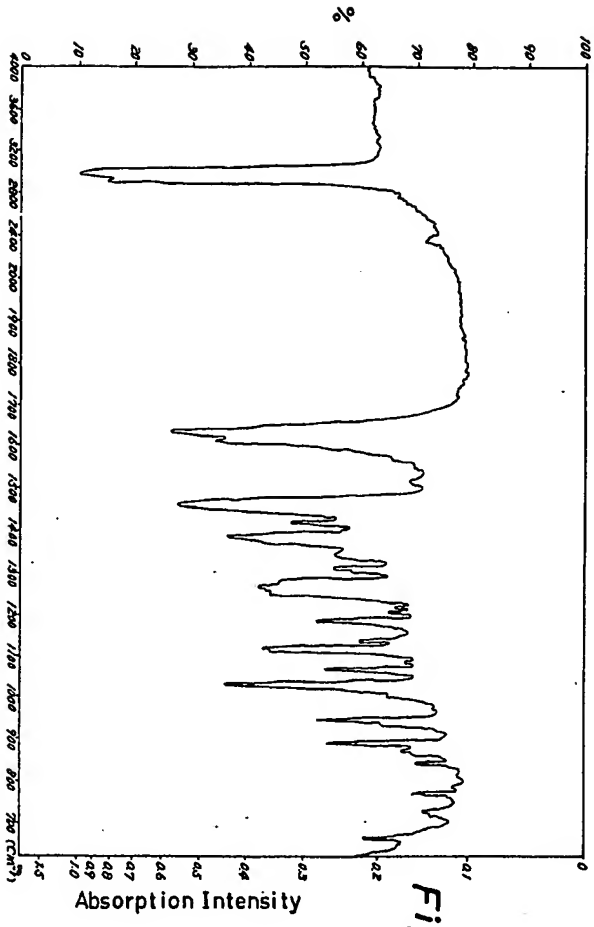


Fig. 2